

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of respiratory rehabilitation on patients with novel coronavirus (COVID-19) pneumonia in the rehabilitation phase: protocol for a systematic review and meta-analysis
AUTHORS	Zhu, Feilong; Zhang, Ming; Gao, Min; Zeng, Cheng; Wang, Dan; Hong, Qianqin; Chen, Wei

VERSION 1 – REVIEW

REVIEWER	Francesco D'Abrosca ARIR - Associazione Riabilitatori dell'Insufficienza Respiratoria
REVIEW RETURNED	06-May-2020

GENERAL COMMENTS	<p>Good idea! Perhaps it may be a little early to find enough scientific papers.</p> <p>If possible, it may be helpful to extend the search beyond April 15, 2020.</p> <p>It would be also interesting to explore if specific lung/chest expansion strategies/exercises and airway clearance techniques/strategies, with or without specific devices, are included in post-Covid PR programs.</p> <p>I suggest to consider also other typical PR outcomes measures of physical performance (6 minute walking distance and other) and quality of life.</p>
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REVIEWER	Giancarlo Garuti Pulmonary Diseases Unit, Santa Maria Bianca Hospital, , Mirandola, Modena, AuslModena, Italy
REVIEW RETURNED	10-May-2020

GENERAL COMMENTS	<p>The purpose of the authors in this protocol (a systematic literature review) is to assess the effects of respiratory rehabilitation on COVID 19 patients.</p> <p>Abstract: in the abstract there is a two times that they do not need the request to the ethical committee because it is a review: the concept is correct, but just insert it in the paragraph of ethics and dissemination.</p> <p>The introduction is consistent with what the protocol wants to evaluate.</p> <p>The search strategy seems correct.</p> <p>Participants : authors should specify if they include either patients treated in ICU, or intermediate respiratory unit and not just those in general ward or in a rehabilitation facility</p> <p>Outcomes</p> <p>The results are unclear: the authors limited the outcomes on spirometric or breathlessness. Data. Please note that COVID 16 patients who are discharged have a high state of physical</p>
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	deconditioning, so outcomes should focus on 6 MWD (if carried out), on nutritional status (BMI) parameters too. The PaO ₂ /FiO ₂ ratio should also be included in the eligibility criteria both at the admission of the rehabilitation programme and at the discharge (of course if indicated by the authors of the studies) Statistical methodology is acceptable
REVIEWER	Mara Paneroni ICS Maugeri Italy
REVIEW RETURNED	18-May-2020
GENERAL COMMENTS	<p>The study describes a protocol for a systematic review and meta-analysis on the effects of respiratory rehabilitation for COVID-19 patients.</p> <p>Although the subject is very interesting, in my opinion there are some relevant aspects that do not allow the publication of the article at this time:</p> <p>a) there are no original studies in the literature on this topic (no randomized controlled trials, but also no pilot studies). For this reason, I think this publication is very premature and not supported by any research data.</p> <p>b) the outcome measures included are not in line with the main outcome measures of pulmonary rehabilitation studies. Despite the rehabilitation could improve lung function or gas exchange at rest, the main expected improvements are on effort tolerance and quality of life. The authors did not take these measures into account.</p> <p>c) I found lack of references (on scales, interventions and so on).</p> <p>d) About intervention: in a pulmonary rehabilitation program one of the most important treatment is the exercise training (endurance and strength). I think that this point have to be evaluated in this kind of studies.</p>

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment 1: Good idea! Perhaps it may be a little early to find enough scientific papers.

If possible, it may be helpful to extend the search beyond April 15, 2020.

Reply 1: Thanks to the reviewer for approving our idea, and thank you for this insightful comment, with which we totally agree. This is a protocol for a systematic review and meta-analysis, and we do not know when there will be enough scientific papers, thus, according to your suggestions, we will not limit the search time in the paper at present, and we will keep a close eye on the progress of respiratory rehabilitation for COVID-19. Once there are enough scientific papers, we will update our registrations on the International Prospective Register of Systematic Reviews (PROSPERO) platform, and carry out this meta-analysis. Meanwhile, to search enough scientific papers, reference lists of relevant trials and reviews will be searched. We will manually search gray literature, such as trial registries.

Changes in the text: "The PubMed, Embase, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Wanfang Data, and VIP information databases will be searched

from inception time to date without restricting research types to find relevant studies. We will also look into reference lists of relevant trials and reviews, and manually search gray literature, such as trial registries." (see Page 2, line 31-36).

Comment 2: It would be also interesting to explore if specific lung/chest expansion strategies/exercises and airway clearance techniques/strategies, with or without specific devices, are included in post-Covid PR programs.

Reply 2: We totally agree with you and thank you for your advice. We have added the suggestions you mentioned to our manuscripts. We referred and cited the following literature, and interventions you mentioned have been added to this study, including active circular breathing technique (ACBT), chest expansion exercises, forced exhalation technique, airway clearance techniques, positive expiratory pressure, using mechanical devices (e.g. mechanical cough assist), exercise training (aerobic exercise, resistance and endurance training). We also adjusted the search strategy appropriately.

Lazzeri M, Lanza A, Bellini R, et al. Respiratory physiotherapy in patients with COVID-19 infection in acute setting: a Position Paper of the Italian Association of Respiratory Physiotherapists (ARIR). *Monaldi Arch Chest Dis* 2020;90(1).

D'Abrosca F, Garabelli B, Savio G, et al. Comparing airways clearance techniques in chronic obstructive pulmonary disease and bronchiectasis: positive expiratory pressure or temporary positive expiratory pressure? A retrospective study. *Braz J Phys Ther* 2017;21(1):15-23.

Paneroni M, Simonelli C, Vitacca M, et al. Aerobic Exercise Training in Very Severe Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. *Am J Phys Med Rehabil* 2017;96(8):541-48.

Changes in the text: "active circular breathing technique, chest expansion exercises, forced exhalation technique, airway clearance techniques, positive expiratory pressure, using mechanical devices (e.g. mechanical cough assist), exercise training (aerobic exercise or, resistance and endurance training), or other physical training programs." (see Page 7, line 125-129).

Table 1 Search strategy of PubMed: "

"Respiratory rehabilitation"[Title/Abstract] OR "pulmonary rehabilitation"[Title/Abstract] OR "Respiratory therapy"[Title/Abstract] OR "pulmonary recovery"[Title/Abstract] OR "pulmonary rehabilitation program"[Title/Abstract] OR "physiotherapy"[Title/Abstract] OR "physical therapy"[Title/Abstract] OR "physical intervention"[Title/Abstract] OR "physical rehabilitation"[Title/Abstract] OR "pulmonary Therapy"[Title/Abstract] OR "pulmonary intervention"[Title/Abstract] OR "respiratory intervention"[Title/Abstract] OR "breath*" [Title/Abstract] OR "exercis*" [Title/Abstract] OR "train*" [Title/Abstract] OR "fitness*" [Title/Abstract] OR "aerobic" [Title/Abstract] OR "resistanc*" [Title/Abstract] OR "endurance" [Title/Abstract] OR "inspiratory muscle train*" [Title/Abstract] OR "inspiratory muscle strength" [Title/Abstract] OR "respiratory muscle train*" [Title/Abstract] OR "respiratory muscle strength" [Title/Abstract] OR "respiratory muscle endurance" [Title/Abstract] OR "muscle relaxation therapy" [Title/Abstract] OR "hydrotherapy" [Title/Abstract] OR "swim*" [Title/Abstract] OR "bik*" [Title/Abstract] OR "joy*" [Title/Abstract] OR "walk*" [Title/Abstract] OR "run*" [Title/Abstract] OR "danc*" [Title/Abstract] OR "sport*" [Title/Abstract] OR "active circular breathing technique" [Title/Abstract] OR "ACBT" [Title/Abstract] OR "chest expansion" [Title/Abstract] OR "forced exhalation technique" [Title/Abstract] OR "airway clearance" [Title/Abstract] OR "mechanical cough assist" [Title/Abstract] OR "manual technique" [Title/Abstract] OR "mechanical device" [Title/Abstract] OR "positive expiratory pressure" [Title/Abstract] OR "power breath" [Title/Abstract]

" (see Page 6, line 107).

Comment 3 : I suggest to consider also other typical PR outcomes measures of physical performance (6 minute walking distance and other) and quality of life.

Reply 3: That's a very good suggestion. Following your advice, we have added 6-minute walking distance (6MWD), cardiopulmonary exercise test (CPET), quality of life (e.g. St. George respiratory questionnaire, SF-36, WHOQOL-100) to our outcomes.

Changes in the text: "The primary outcomes of interest will be 6-minute walking distance (6MWD), cardiopulmonary exercise test (CPET), quality of life. The secondary outcomes are as follows: body mass index, arterial partial pressure of oxygen/fraction of inspired oxygen (PaO₂/FiO₂) ratio, forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), ratio of forced expiratory volume in one second and forced vital capacity (FEV₁/FVC), baseline dyspnea index (BDI), rating of perceived exertion scale scores, Borg scale scores, blood oxygen saturation, and discharge time." (see Page 7, line 132-140).

Reviewer: 2

Comment 1: Abstract: in the abstract there is a two times that they do not need the request to the ethical committee because it is a review: the concept is correct, but just insert it in the paragraph of ethics and dissemination.

Reply 1: I am sorry for the mistake, and we have modified this as advised.

Changes in the text: (see Page 2, line 28-29).

Comment 2: Participants: authors should specify if they include either patients treated in ICU, or intermediate respiratory unit and not just those in general ward or in a rehabilitation facility.

Reply 2: Thank you for your advice. I am sorry for this, and we have modified this as advised. We have made a detailed description of the included participants in the manuscript. We will include patients who suffered from viral pneumonia caused by the coronavirus disease 2019 and coordinated with respiratory rehabilitation treatments regardless of section, whether in the intensive care unit (ICU), intermediate respiratory unit, general ward, or rehabilitation facility will be involved in this meta-analysis. If necessary, subgroup analyses will be performed in different treatment locations. There will be no restrictions with respect to gender, age, or ethnicity. Also, we will update our registrations on the International Prospective Register of Systematic Reviews (PROSPERO) platform.

Changes in the text: "Patients who suffered from viral pneumonia caused by the coronavirus disease 2019 and coordinated with respiratory rehabilitation treatments regardless of section, whether in the intensive care unit (ICU), intermediate respiratory unit, general ward, or rehabilitation facility will be involved in this meta-analysis. There will be no restrictions with respect to gender, age, or ethnicity." (see Page 7, line 116-121).

Comment 3: The results are unclear: the authors limited the outcomes on spirometric or breathlessness. Please note that COVID 19 patients who are discharged have a high state of physical deconditioning, so outcomes should focus on 6 MWD (if carried out), on nutritional status (BMI) parameters too. The PaO₂/FiO₂ ratio should also be included in the eligibility criteria both at the admission of the rehabilitation programme and at the discharge (of course if indicated by the authors of the studies).

Reply 3: I am sorry for the mistake, and we have modified this as advised. Following your advice, we have added 6-minute walking distance (6MWD), body mass index (BMI), arterial partial pressure of

oxygen/fraction of inspired oxygen (PaO₂/FiO₂) ratio to our outcomes.

Changes in the text: “The primary outcomes of interest will be 6-minute walking distance (6MWD), cardiopulmonary exercise test (CPET), quality of life. The secondary outcomes are as follows: body mass index, arterial partial pressure of oxygen/fraction of inspired oxygen (PaO₂/FiO₂) ratio, forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), ratio of forced expiratory volume in one second and forced vital capacity (FEV₁/FVC), baseline dyspnea index (BDI), rating of perceived exertion scale scores, Borg scale scores, blood oxygen saturation, and discharge time.” (see Page 7, line 131-140).

Reviewer: 3

Comment 1: There are no original studies in the literature on this topic (no randomized controlled trials, but also no pilot studies). For this reason, I think this publication is very premature and not supported by any research data.

Reply 1: Thank you for this insightful comment. Your concern is exactly what we are worried about. At present, COVID-19 virus has sparked a pandemic around the world and millions of people have been infected. This is a protocol for a systematic review and meta-analysis, and we do not know when there will be enough scientific papers. We will not limit the search time in the paper at present, and we will keep a close eye on the progress of respiratory rehabilitation for COVID-19. Once there are enough scientific papers, we will update our registrations on the International Prospective Register of Systematic Reviews (PROSPERO) platform, and carry out this meta-analysis. Meanwhile, to search enough original studies, reference lists of relevant trials and reviews will be searched. We will manually search gray literature, such as trial registries. We believe there will be more original studies in the literature on this topic appearing. Just as BMJ Open journal state that “publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicized. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study”. Thanks again for your insightful comment.

Changes in this text: “The PubMed, Embase, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Wanfang Data, and VIP information databases will be searched from inception time to date without restricting research types to find relevant studies. We will also look into reference lists of relevant trials and reviews, and manually search gray literature, such as trial registries.” (see Page 2, line 31-36).”

Comment 2: The outcome measures included are not in line with the main outcome measures of pulmonary rehabilitation studies. Despite the rehabilitation could improve lung function or gas exchange at rest, the main expected improvements are on effort tolerance and quality of life. The authors did not take these measures into account.

Reply 2: I am sorry for the mistake, and we have modified this as advised. Following your advice, we have added 6-minute walking distance (6MWD), cardiopulmonary exercise test (CPET), quality of life to our outcomes.

Changes in this text: “The primary outcomes of interest will be 6-minute walking distance (6MWD), cardiopulmonary exercise test (CPET), quality of life. The secondary outcomes are as follows: body mass index, arterial partial pressure of oxygen/fraction of inspired oxygen (PaO₂/FiO₂) ratio, forced

expiratory volume in one second (FEV1), forced vital capacity (FVC), ratio of forced expiratory volume in one second and forced vital capacity (FEV1/FVC), baseline dyspnea index (BDI), rating of perceived exertion scale scores, Borg scale scores, blood oxygen saturation, and discharge time.”(see Page 7, line 131-140).

Comment 3: I found lack of references (on scales, interventions and so on).

Reply 3: I am sorry for this, and we have modified this as advised. We referred and cited the following literature on the outcomes, interventions, and some statistical methodologies. The partial literature are as follows:

Lazzeri M, Lanza A, Bellini R, et al. Respiratory physiotherapy in patients with COVID-19 infection in acute setting: a Position Paper of the Italian Association of Respiratory Physiotherapists (ARIR). *Monaldi Arch Chest Dis* 2020;90(1).

Paneroni M, Simonelli C, Vitacca M, et al. Aerobic Exercise Training in Very Severe Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. *Am J Phys Med Rehabil* 2017;96(8):541-48.

Yang F, Liu N, Hu JY, et al. [Pulmonary rehabilitation guidelines in the principle of 4S for patients infected with 2019 novel coronavirus (2019-nCoV)]. *Zhonghua Jie He He Hu Xi Za Zhi* 2020;43(3):180-82.

Paneroni M, Simonelli C, Saleri M, et al. Short-Term Effects of Normocapnic Hyperpnea and Exercise Training in Patients With Chronic Obstructive Pulmonary Disease: A Pilot Study. *Am J Phys Med Rehabil* 2018;97(12):866-72.

Hoffman M, Chaves G, Ribeiro-Samora GA, et al. Effects of pulmonary rehabilitation in lung transplant candidates: a systematic review. *BMJ Open* 2017;7(2):e013445.

He M, Yu S, Wang L, et al. Efficiency and safety of pulmonary rehabilitation in acute exacerbation of chronic obstructive pulmonary disease. *Med Sci Monit* 2015;21:806-12.

Comment 4: About intervention: in a pulmonary rehabilitation program one of the most important treatment is the exercise training (endurance and strength). I think that this point have to be evaluated in this kind of studies.

Reply 4: We totally agree with you and thank you for your advice. We have added the suggestions you mentioned to our manuscripts. Exercise training (aerobic exercise, resistance, and endurance training) will be evaluated in this study. We also adjusted the search strategy appropriately to search studies about effects of exercise training for patients with novel coronavirus (COVID-19) pneumonia.

Changes in this text: “exercise training (aerobic exercise or, resistance and endurance training), or other physical training programs.” (see Page 7, line 128-129).

Table 1 Search strategy of PubMed: “

“Respiratory rehabilitation”[Title/Abstract] OR “pulmonary rehabilitation”[Title/Abstract] OR “Respiratory therapy”[Title/Abstract] OR “pulmonary recovery”[Title/Abstract] OR “pulmonary rehabilitation program”[Title/Abstract] OR “physiotherapy”[Title/Abstract] OR “physical therapy”[Title/Abstract] OR “physical intervention”[Title/Abstract] OR “physical rehabilitation”[Title/Abstract] OR “pulmonary Therapy”[Title/Abstract] OR “pulmonary intervention”[Title/Abstract] OR “respiratory intervention”[Title/Abstract] OR “breath*”[Title/Abstract]

OR "exercis*"[Title/Abstract] OR "train*"[Title/Abstract] OR "fitness*" [Title/Abstract] OR
"aerobic"[Title/Abstract] OR "resistanc*" [Title/Abstract] OR "endurance"[Title/Abstract] OR "inspiratory
muscle train*"[Title/Abstract] OR "inspiratory muscle strength" [Title/Abstract] OR "respiratory muscle
train*"[Title/Abstract] OR "respiratory muscle strength"[Title/Abstract] OR "respiratory muscle
endurance" [Title/Abstract] OR "muscle relaxation therapy" [Title/Abstract] OR "hydrotherapy"
[Title/Abstract] OR "swim*" [Title/Abstract] OR "bik*" [Title/Abstract] OR "joy*" [Title/Abstract] OR
"walk*" [Title/Abstract] OR "run*" [Title/Abstract] OR "danc*" [Title/Abstract] OR "sport*" [Title/Abstract]
OR "active circular breathing technique" [Title/Abstract] OR "ACBT" [Title/Abstract] OR "chest
expansion" [Title/Abstract] OR "forced exhalation technique" [Title/Abstract] OR "airway
clearance" [Title/Abstract] OR "mechanical cough assist" [Title/Abstract] OR "manual
technique" [Title/Abstract] OR "mechanical device" [Title/Abstract] OR "positive expiratory
pressure" [Title/Abstract] OR "power breath" [Title/Abstract]"
(see Page 6, line 107).